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Inflammatory Bowel Disease Cancer Risk, Detection and Surveillance

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Key Words
Ulcerative colitis · Cancer risk · Surveillance · Dysplasia · Intraepithelial neoplasia · Colonoscopy · Chromoendoscopy

Abstract
Ulcerative colitis (UC) is a chronic and relapsing inflammation of the colonic mucosa with variable extension from the rectum towards the cecum. The aim of medical treatment is to induce and maintain clinical remission. If no remission can be achieved, continuous inflammation may repeatedly destroy the epithelial cells. This has to be compensated by epithelial increased proliferation which finally can lead to inflammation-associated colorectal cancer (CRC). The risk of colitis-associated CRC is increased after a long disease duration, especially in patients with chronic active disease. This risk may be lower if long-lasting mucosal healing can be achieved. To detect the development of dysplasia/intraepithelial neoplasia and colitis-associated CRC early, surveillance programs have been installed. However, the evidence of success for those surveillance programs is limited. This is partially due to problems of detecting precancerous lesions in the colonic mucosa during those surveillance programs. The specific problems of surveillance programs for the prevention of CRC and specific aspects of patient care in UC are reviewed in this article.

Risk of Colorectal Carcinoma in Patients with Ulcerative Colitis

It is well accepted that ulcerative colitis (UC) is associated with an increased risk of developing colorectal cancer (CRC). As the molecular pathways that change during the progression from normal epithelia to dysplasia and finally cancer are different from sporadic CRC, the term 'colitis-associated cancer' is frequently used. It has been estimated in older studies that the risk for this inflammation-associated CRC in UC patients is about 7% at 20 years of disease [1–3], 7–14% at 25 years [4, 5] and as high as 30% after 35 years. In more recent studies, lower risks have been reported.

In a 2001 meta-analysis based on 116 studies with 54,478 patients, Eaden et al. [6] showed that there is an increased risk of cancer in pancolitis as compared to left-sided colitis (fig. 1). The overall prevalence of CRC in any patient with UC was shown to be 3.7%, and 5.4% in patients with pancolitis [6]. The cumulative CRC risk for any patient with UC was 2% at 10 years, 8% at 20 years and 18% at 30 years [6] (fig. 1). As the background risk in the normal population is about 5% during lifetime, this means that the risk of developing CRC at 30 years after initial diagnosis of UC is three- to fourfold increased at least. In ulcerative proctitis, the cancer risk appeared not to be increased.

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In a recent analysis in Denmark, no increased incidence of CRC was found [7]. Neither the overall cancer risk nor the CRC risk was increased in this population-based cohort in Copenhagen County after a median of 19 years of follow-up evaluation. This surprising finding, however, may be due to the higher rates of colectomy in this country and cohort, respectively [7]. In a large cohort of patients with extensive UC (600 patients over a 30-year period of observation), Rutter et al. [8] reported cumulative incidences of CRC by colitis duration of 2.5% at 20 years, 7.6% at 30 years and 10.8% at 40 years. Only 30 of 600 patients (5%) developed CRC [8]. A recent Swedish analysis including 7,607 patients with UC diagnosed between 1954 and 1989 investigated frequency of CRC through 2004. The study indicated that over the past 35 years the risk of death from CRC declined markedly [9] (table 1).

Most recently, Jess et al. [10] performed a meta-analysis on population-based studies. In their analysis, an average of 1.6% of patients with UC were diagnosed with CRC during 14 years of follow-up [10]. Men with UC had a greater risk of CRC as compared to women. In the population-based (unbiased and unselected cohorts), the diagnosis of UC increased the risk of CRC 2.4-fold (which is clearly lower as compared to the data from Eaden et al. [6]). The direct comparison of the data from Eaden et al. [6] and Jess et al. [10] makes the differences obvious: in contrast to the above-mentioned cumulative incidences of CRC of 2% at 10 years and 8% at 20 years of follow-up for any patient with UC, these figures were only 0.4 and 1.1–5.3%, respectively, in the meta-analysis by Jess et al. [10]. The analysis of nonpopulation-based data derived from specialized centers may have introduced some selection bias into the analyses. The lower incidence of CRC in UC patients in more recent studies has also been explained with better control of inflammation and higher rates of mucosal healing. As this is hard to prove in clinical studies, it will remain speculative.

The CRC risk increases with the duration of the disease and correlates positively with the severity of inflammation and extent of the disease [6, 11–16]. In fact, there is no uniform and general accepted definition of disease duration. Onset of symptoms has generally been used as starting point for disease duration in the studies that have identified this parameter as a risk factor [17]. Based on the meta-analysis by Eaden et al. [6], it is assumed that the risk for CRC begins to increase 8–10 years after onset of inflammation.

The risk of developing CRC is further increased in patients with primary sclerosing cholangitis (PSC) [18–27].

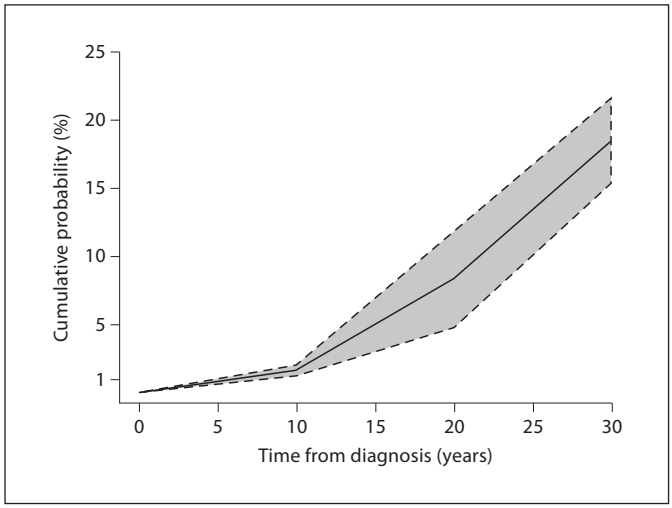

Fig. 1. Meta-analysis of 116 studies assessing the risk of CRC in CU patients [6]. Cumulative risk of developing CRC: 2% at 10 years, 8% at 20 years and 18% at 30 years.

Table 1. Risk of CRC in 3 population-based Swedish cohorts (1954–1989) including 7,607 patients with IBD (198,227 patient-years)

	10 years	20 years	30 years
Pancolitis	1.5	3.8	7.6
UC	1	2.3	5.2
CD	0.5	1.4	2.2

196 CRCs were found in 188 patients [9].

Myths and Facts about Surveillance Colonoscopy

Generally, it is believed that the colitis-associated mortality of CRC can be reduced by surveillance colonoscopy. Colonoscopic surveillance for dysplasia once a year or every 2 years with random biopsies has been advocated in many countries and in most guidelines [16, 17, 28–31]. Collins et al. [32] published a Cochrane database systematic review in 2006. For their analysis, they focused on 11 studies attempting to address the impact of surveillance colonoscopy on survival of patients with UC. Six of these studies were retrospective analyses lacking control groups. Three case control studies performed by Karlen et al. [33] in 1998 on 4,664 patients, Choi et al. [34] in 1993 and Lashner et al. [35] in 1990 are discussed in detail. In the first study, 2 out of 40 patients that died on CRC had

undergone surveillance colonoscopy on at least one occasion as compared with 18 out of 102 of the controls [33]. This difference, however, did not reach statistical significance (RR = 0.29, 95% CI: 0.06–1.31) [33]. In the study by Choi et al. [34], a total of 41 patients developed carcinoma: 19 had undergone colonoscopy surveillance and 22 had not. The 5-year survival rate was 77.2% for cancer of the surveillance group and 36.3% for the non-surveillance group (p = 0.026), indicating that the cancers in the control group were more advanced as compared to the cancers in the surveillance group [34]. In the study by Lashner et al. [35], 4 out of 91 patients in the surveillance group died from CRC as compared to 2 out of 95 patients in the non-surveillance group, with no difference seen between those groups. It has to be mentioned, however, that the benefit of surveillance could have been higher in these studies if multiple biopsies had been performed. From the data outlined, no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis can be obtained [32]. However, it may be concluded that cancers are detected at an earlier stage in patients who are undergoing surveillance, and that these patients have a correspondingly better prognosis [32]. Overall, the Cochrane review is very cautious in its statements pointing to indirect evidence that surveillance is likely to be effective in reducing the risk of death from inflammatory bowel disease-associated CRC and indirect evidence that it may be acceptably cost-effective [32]. Therefore, also in the ECCO guidelines, the recommendation for surveillance is not strong. In the article by Biancone et al. [17] it is stated – similar to the Cochrane review – that surveillance colonoscopy may permit earlier detection of CRC, with a corresponding improved prognosis. Further, it is noted that unequivocal evidence showing surveillance colonoscopy prolongs survival in patients with UC is lacking [17].

When and How Should Surveillance Colonoscopy Be Performed?

Generally, it is recommended that for surveillance all colitis patients should undergo a complete ileocolonoscopy 8–10 years after the initial symptoms [17]. As outlined above, this recommendation is mainly based on meta-analyses that downscale the wide variation in reported CRC risk in different studies [6, 36]. It should be emphasized here that this time-point is referred to the initial symptoms and not to the first diagnosis, as patients might have had the disease for several years before being diagnosed. In patients with extensive colitis, it is recommended that surveillance should start after screening colonoscopy (8–10 years after onset of disease) and then be performed every other year up to year 20 of disease, then annually or annually from 10 years of disease duration on [16, 17, 30, 31, 37].

In patients with left-sided colitis, also a new staging colonoscopy should be performed 8 years after disease onset to identify patients with a spreading of inflammation from left-sided to more extensive disease. Patients who still have left-sided colitis should start surveillance 15 years after first manifestation [16, 17, 30, 31, 37]. Patients with extension to pancolitis should have their surveillance colonoscopy every 2 years after the index colonoscopy at 8 years (as mentioned above for extensive disease). In all guidelines the consensus on this strategy is strong [17, 31, 37] despite the lack of robust efficacy data.

If PSC is present, annual surveillance colonoscopies should be started independent of the disease activity and extent right after the diagnosis of UC and PSC. In patients with PSC, the risk of developing a CRC is particularly high and has been reported to occur early (median 2.9 years) after symptom onset [19, 20, 23, 38–42]. Despite robust data showing a clear advantage of this strategy, it is obvious that these patients at high risk for CRC should enter a more intensive surveillance program once diagnosed.

The Cochrane review clearly showed that surveillance colonoscopy cannot completely abolish the risk of CRC in patients with UC [32]. However, it is likely that those CRCs are detected earlier, thus improving the 5-year survival rate as indicated above. On the other hand, a study from the Netherlands indicated that up to 20% of patients may have a colitis-associated CRC before the index colonoscopy at 8 years after symptom onset [43]. If the patients with concomitant PSC are subtracted from this group, the frequency of CRC occurring without this risk factor before the 8-year margin is still an alarming 10–15%. The severity of inflammation may be relevant with respect to this [12, 44, 45]. Therefore, it may be justified to include patients with chronically active disease in a surveillance program earlier. The interval between two surveillance colonoscopies should be longer than 2 years, as carcinoma might occur in this time-frame interval [46].

Despite the fact that ulcerative proctitis might have a slightly increased risk of carcinoma [47], there is no consensus on regular proctologic examination. In a study by Söderlund et al. [9], the risk of CRC was much greater in patients with UC pancolitis (SIR: 5.6; 95% CI: 4.4–7.0)

when compared with the general population. The standardized incidence ratio was lower when compared to UC patients with proctitis, raising the possibility that UC proctitis might be associated with an increased risk of CRC [47].

How Should Surveillance Colonoscopies Be Performed?

Crucial factors for surveillance colonoscopies are on one hand the number of biopsies taken and on the other hand the time taken for the evaluation of the colon. A further important point is with respect to the conditions of the colonoscopy, i.e. whether the cleansing of the gut has been done successfully [48]. If the conditions of the colonoscopy are not perfect due to feces still being present, the colonoscopy should be repeated [48]. Further, it appears to be important that the colonoscopy is done during a remission phase of the colitis as the histomorphological discrimination of inflamed and neoplastic changes is difficult. Low-grade dysplasia may be missed as inflamed mucosa is present or, on the other hand, inflamed mucosa may be misinterpreted as dysplastic mucosa [49]. Of course, the general aim of surveillance colonoscopies is to detect neoplasias with high sensitivity and specificity. Macroscopic evaluation of the gut is therefore very helpful [50, 51]. It has even been stated that upon excellent preparation most lesions will be macroscopically visible [50, 52]. If the mucosa is inflamed, the macroscopic evaluation is difficult [49].

Targeted biopsies should be taken from all endoscopically suspect lesions [50–52]. In addition, blind and nontargeted biopsies should be taken every 4 cm in all quadrants as up to 20% of dysplastic lesions may not be visible macroscopically. Mathematical modeling was done by Rubin et al. [53] indicating that 34 random biopsies will result in a 90% CI to detect CRC or high-grade dysplasia, 64 biopsies will be necessary for a 95% probability of detection. Despite the fact that this is only a model based on a questionable basis and that the evidence is weak, similar numbers for random biopsies during surveillance colonoscopy can now be found in a number of guidelines [31, 37]. To achieve a 90% security for the detection of dysplasia/neoplastic lesions, it is recommended that 4 biopsies are taken every 10 cm. In 2003, Kiesslich et al. [54] found only 2 intraepithelial neoplasias in 598 random biopsies, and in 2004 Rutter et al. [55] did not detect any intraepithelial neoplasias in 2,906 random biopsies. As with the new techniques of high-resolution endoscopy, lesions may be visible much better than in former eras [50, 52]; however, this point is still a matter of discussion. In reality, the number of random biopsies taken during surveillance colonoscopy in UC patients is usually much lower [29].

As an alternative, chromoendoscopy with targeted biopsies in all suspect areas may be recommended [55–58]. The advantages of chromoendoscopy were recently confirmed in a multicenter study which detected more intraepithelial neoplasia as compared to conventional colonoscopy [59]. However, it should be kept in mind that methylene blue, which is frequently recommended for chromoendoscopy, may cause DNA damage and contribute to CRC risk [60–62]. Therefore, indigo carmine seems to be the better alternative for chromoendoscopy [55, 60, 63]. The other techniques that have been investigated in recent years should not be used as stand-alone strategies.

A number of studies in recent years could demonstrate that the higher number of intraepithelial neoplasias can be detected with high-resolution endoscopy [64]. Irregular mucosa structures or elevated areas of the mucosa might be detected [65, 66]. Presently, however, the published data are not sufficient to completely omit the recommendation for random biopsies. As a potential replacement of chromoendoscopy, virtual chromoendoscopy techniques such as NBI, FICE or I-SCAN have been recommended; however, the data published so far are inconclusive [67–70].

What to Do if Dysplasia/Intraepithelial Neoplasia Has Been Found?

If an intraepithelial neoplasia is detected, there should be an external and independent second opinion by a pathologist [16, 17, 30, 31, 37]. The presence of a low-grade intraepithelial neoplasia should be reinvestigated by colonoscopy control after an increase of anti-inflammatory therapy within 3 months.

The grading of the intraepithelial neoplasias is very important for the CRC risk in patients with UC. When a patient undergoes colectomy due to CRC, random biopsies in the colectomy specimen detect intraepithelial neoplasia in up to 74% [71]. This indicates that there may be several additional neoplasias in UC colon that have already developed CRC at one location. A meta-analysis has shown that in low-grade intraepithelial neoplasias and low-grade dysplasia, the risk for CRC is at least ninefold [72]. Therefore, the detection of low-grade dysplasia and low-grade intraepithelial neoplasias has important

consequences for further treatment. However, there is a high interobserver variability among pathologists [73]. The variability is especially high for low-grade dysplasia [73]. Due to the therapeutic consequences, therefore, an independent second opinion is mandatory. In the meta-analysis by Thomas et al. [72] based on 20 studies with 508 patients with low-grade dysplasia, an up to 12-fold risk of developing advanced lesions such as high-grade dysplasia or CRC as compared to patients without low-grade dysplasia was found [72]. The positive protective value for low-grade dysplasia including DALM for concurrent advanced lesions was 37%. The positive protective value for low-grade dysplasia in the presence of a DALM for concurrent advanced lesions was 41% [72]! If a second external pathologist confirms the diagnosis of low-grade dysplasia or low-grade intraepithelial neoplasia, the patient should be informed about his risk and proctocolectomy should be recommended. As an alternative, a tight surveillance colonoscopy program every 3 months might be acceptable. Adenoma-associated dysplasia, however, has to be treated differently. A clear adenoma-like lesion with intraepithelial neoplasia, which is classified as adenoma-associated dysplasia by the pathologist, should be resected endoscopically.

Disclosure Statement

Gerhard Rogler has consulted Abbott Switzerland and Abbott International, FALK Germany, Essex/MSD Switzerland, Novartis, Roche, Tillotts and Vifor Switzerland and has received speaker's honoraria from Abbott, FALK, MSD, Tillotts, UCB, and Vifor. He has also received educational grants and research grants from Abbott, Ardeypharm, Essex/MSD, FALK, Flamentera, Novartis, Tillotts, UCB and Zeller.

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